REMARKS

In view of the above amendments and the following remarks, the Examiner is requested to allow claims 1-35, 67-101 and 144-149, the only claims pending and under examination in this application.

Claim Rejections – 35 U.S.C. § 103

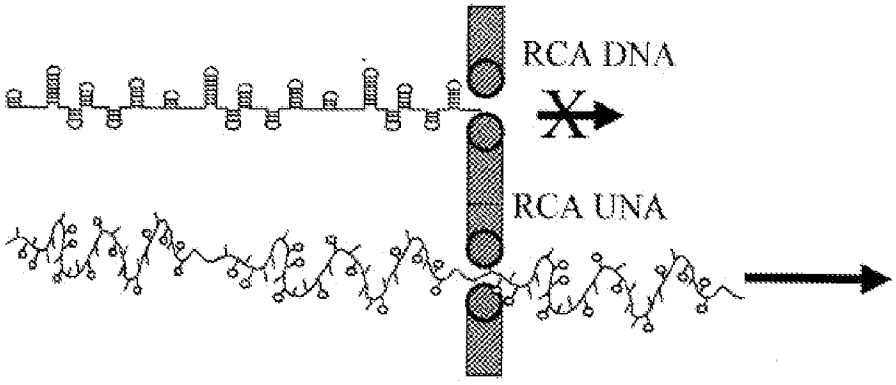
Claims 1-5, 8-34, 67-71, 74-100 and 144-147 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Church et al. (U.S. Patent No. 5,795,782) in view of Morgan et al. (*Biochemistry*, 1980, vol. 19, no. 26, p. 5960-66), and further in view of Kutyavin et al. (U.S. Patent No. 5,912,340).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007))); *and see Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (*citing KSR Int'l Co.* at 1741)); *and see Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

Independent Claims 1 and 67 include the element that "the nucleic acid molecule contains at least two different complementary base pair analogs, wherein the at least two different complementary base pair analogs comprise modified nucleotides that reduce secondary structure in the nucleic acid molecule".

In making this rejection, the Examiner alleges that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of modified bases by Church in view of Morgan to replace adenine and thymine in the nucleic acids of the invention to include the 2-aminoadenine and 2-thiothymine of Kutyavin to arrive at the claimed invention with a reasonable expectation of success." Office Action, pg. 11, lines 3-7. In addition, the Examiner states that, "While neither Church or Morgan teaches the inclusion of analogues for A and T, Kutyavin teaches analogues for each nucleotide monomer and the reduction of hydrogen bonding stability." Office Action, pg. 11, lines 14-16.

The Applicants respectfully disagree. As shown below, Figure 6 of the present application depicts nanopore sequencing of nucleic acid molecules with secondary structure and nanopore sequencing of unstructured nucleic acid molecules. Application Specification, pg. 10, line 22 to pg. 11, line 2.



In contrast, Kutyavin actually discloses that, "A sufficient number of the modified SBC nucleotides are incorporated such that complementary positions in both SBC ODNS are modified into a matched pair of SBC ODNs of the present invention so that the pair of the matched set does not form a stable hybrid". Kutyavin, col. 4, lines 39-43. As such, Kutyavin merely suggests substituting enough positions in two oligonucleotides to prevent binding to prevent binding between the oligonucleotides. However, nowhere does Kutyavin disclose or suggest anything about secondary structure or substituting complementary positions in a single oligonucleotide. As such, Kutyavin fails to disclose or suggest to a person of skill in the art substituting complementary positions within a single nucleic acid with UNA nucleotides.

At the time of filing of this application, unstructured nucleic acid (UNA) nucleotides were known and had been proposed for reducing the T_m of *inter*-molecular interactions between UNA-containing nucleic acids (see e.g., Kutyavin). Prior to the filing date, however, there was no recognition in the art that UNA nucleotides could decrease *intra*-molecular interactions within one nucleic acid (i.e., no recognition that UNA nucleotides could be used to decrease the secondary structure of a nucleic acid).

The use of UNA nucleotides to decrease *intra*-molecular interactions rather than *inter*-molecular interactions is captured in the claims in that they recite that "the nucleic acid molecule contains at least two different complementary base pair analogs, wherein the at least two different complementary base pair analogs comprise modified nucleotides that reduce secondary structure in the nucleic acid molecule". Conceptually, this can be thought of as a new use for UNA nucleotides.

The use of UNA nucleotides to decrease *intra*-molecular interactions might in hindsight initially appear to be a straightforward extension of prior art methods. However, the Applicants believe that it is not an extension that would have been made by one of skill in the art without the hindsight of the Applicants' disclosure. Recognition that UNA nucleotides could be used to decrease *intra*-molecular interactions, in addition to *inter*-molecular interactions, required innovation rather than ordinary skill and common sense.

The use of UNA nucleotides to decrease *intra*-molecular interactions is neither taught nor suggested by Kutyavin or the prior art. Moreover, prior art solutions for decreasing secondary structure typically included substituting a single type of modified nucleotide into a sequence (e.g., substituting inosine in place of guanine, for example) because substituting more than a single type of nucleotide in a nucleic acid would result in drastically decreased specificity for its target. At best, therefore, one of skill in the art wishing to decrease secondary structure might substitute in one type of UNA nucleotide, rather than a "complementary" pair of UNA nucleotides as is required by the rejected claims.

Moreover, the rejected claims require a nucleic acid that contains at least two different complementary base pair analogs that would otherwise cause secondary structure.

Kutyavin does not teach or reasonably suggest such a nucleic acid and, as such, nowhere does Kutyavin disclose or suggest the element that "the nucleic acid molecule contains at least two different complementary base pair analogs, wherein the at least two different complementary base pair analogs comprise modified nucleotides that reduce secondary structure in the nucleic acid molecule".

Consequently, for the reasons stated above, the cited combination of Church, Morgan and Kutyavin fails to teach or suggest every element of the rejected claims. Accordingly, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1-5, 8-34, 67-71, 74-100 and 144-147 be withdrawn.

Moreover, in *KSR*, the Supreme Court made clear that, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. . . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 127 S. Ct. at 1741. The Supreme Court further explained that, "it will be necessary for a court to look to interrelated teachings of multiple patents . . . in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." *KSR*, 127 S. Ct. at 1740-1741, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

The Applicants submit that one of skill in the art would have had no apparent reason to combine the cited references in the manner suggested by the Examiner. One of skill in the art would have had no apparent reason to combine the references because, as discussed above, Kutyavin is merely directed to *inter*-molecular interactions and discloses oligonucleotides in which "complementary positions in both SBC ODNS are modified into a matched pair of SBC ODNs of the present invention so that the pair of the matched set does not form a stable hybrid". Kutyavin, col. 4, lines 40-43. Thus, one of skill in the relevant art would have had no reason to combine Kutyavin with the disclosures of Church and Morgan to reach the Applicants' claimed element that "the nucleic acid molecule contains at least two different complementary base pair analogs, wherein the at least two different complementary base pair analogs comprise modified nucleotides that reduce secondary structure in the nucleic acid molecule". As such, the Applicants' submit that a *prima facie* case of obviousness cannot be maintained and respectfully request that that the 35 U.S.C. § 103(a) rejection of Claims 1-5, 8-34, 67-71, 74-100 and 144-147 be withdrawn.

Claims 6-7, 72-73 and 148-149 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Church et al. (U.S. Patent No. 5,795,782) in view of Morgan et al. (*Biochemistry*, 1980, vol. 19, no. 26, p. 5960-66), in view of Kutyavin et al. (U.S. Patent No. 5,912,340), and further in view of Lizardi et al. (U.S. Patent No. 6,632,609). As set forth above, the cited combination of Church, Morgan and Kutyavin is deficient in that it fails to disclose or suggest the claimed element that "the nucleic acid molecule contains at least two different complementary base pair analogs, wherein the at least two different complementary base pair analogs comprise modified nucleotides that reduce secondary structure in the nucleic acid molecule". Moreover, as set forth above, one of skill in the relevant art would have had no apparent reason to combine the cited references in the manner suggested by the Examiner. Lizardi was cited solely for its alleged disclosure of the synthesis and amplification of circular nucleic acid templates. Consequently, Lizardi fails to remedy the deficiencies of Church, Morgan ad Kutyavin. Therefore, the cited combination of Church, Morgan, Kutyavin and Lizardi does not disclose or suggest all the elements of Claims 6-7, 72-73 and 148-149, and the Applicants respectfully request withdrawal of this rejection.

Claims 35 and 101 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Church et al. (U.S. Patent No. 5,795,782) in view of Morgan et al. (*Biochemistry*, 1980, vol. 19, no. 26, p. 5960-66), in view of Kutyavin et al. (U.S. Patent No. 5,912,340), and further in view of Thorp et al. (U.S. Patent No. 5,795,782). As set forth above, the cited combination of Church, Morgan and Kutyavin is deficient in that it fails to disclose or suggest the claimed element that "the nucleic acid molecule contains at least two different complementary base pair analogs, wherein the at least two different complementary base pair analogs comprise modified nucleotides that reduce secondary structure in the nucleic acid molecule". Moreover, as set forth above, one of skill in the relevant art would have had no apparent reason to combine the cited references in the manner suggested by the Examiner. Thorp was cited solely for its alleged disclosure of the analysis of nucleic acids by electron tunneling. Consequently, Thorp fails to remedy the deficiencies of Church, Morgan and Kutyavin. Therefore, the cited combination of Church, Morgan, Kutyavin and Thorp does not disclose or suggest all the elements

of Claims 35 and 101, and the Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone James Keddie at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10001492-2.

Respectfully submitted,

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